cells expressing an EphrinB2 protein, which cells differentiate or maintain an arterial phenotype in a manner dependent on the activity of the EphrinB2 protein, and

a test agent;

(b) determining if the agent can interfere with the ability of said EphrinB2 protein to transduce a signal that affects said arterial phenotype; and

(c) administering, to a nonhuman animal, an agent identified in (b), and measuring the anti-angiogenic activity, if any, of said agent.

CM Cont

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." For the convenience of the Examiner, all claims being examined, whether or not amended, are presented in that section.

REMARKS

Claims 46, 47, 49, 50, 77-89, 92, 93, 95-100, 107-108, 114, 120 and 151-155 are pending in the present application. Claims 45, 48, 90, 91, 94, 101-106, 109-113, 115-119 and 121-150 have been cancelled. Applicants respectfully request reconsideration in view of the following remarks.

I. THE CLAIMED SUBJECT MATTER IS PATENTABLE OVER THE ART

Applicants note with appreciation that the Examiner considers the claimed subject matter to be patentable over the prior art. Accordingly, none of the above amendments are made to overcome an issue concerning the prior art.

II. THE PENDING CLAIMS COMPLY WITH 35 USC §112, 1ST PARAGRAPH

The Examiner has rejected claims 45-50 and 77-150 under 35 USC §112, first paragraph, arguing that the specification "*while being enabling for methods of screening for inhibitors of interactions using Eph and Ephrin family members, does not reasonably provide enablement for methods using all artery- and vein-specific proteins, for method of identifying activators, or for methods using 'portions' of Eph and Ephrin family members*". This rejection is respectfully traversed.

In so far as the rejection is based on the claims encompassing signaling pathways other than those mediated by Ephrin/Eph proteins, the current amendments to the claims are believed to obviate the Examiner's rejection. The amendments are not meant to acquiesce to the rejection, but rather are offered as a means to expedite prosecution of claims relating to commercial embodiments currently under development.

With regard to the rejection of those claims reciting "portions" of Ephrin and Eph receptors, the Examiner argues that "*no necessary structural characteristics by which the appropriate 'portions' of Ephs and Ephrins could be identified are set for forth*", asserting that undue experimentation would be required to determine what portions of those molecules could be used in the claimed assays. The rejected claims have been amended to require that, to the extent the claimed assay makes use of a "portion", that portion must retain the function of binding the cognate ligand or receptor, as appropriate.

Applicants assert that no more than routine experimentation is required to identify such functional fragments. Enablement is not precluded even if some experimentation is necessary. Applicants contend that the specification provides sufficient guidance with respect to isolating fragments of Eph and Ephrin proteins having the recited biological properties such that a person of ordinary skill in the art could make and use the claimed assays without undue experimentation, relying on the specification and knowledge in the art.

It was generally well known in the art that the Eph receptors and their ligands (ephrins) are a family of proteins having highly conserved structures. In a number of functional studies, strict conservation of structure and function across distantly related vertebrate species has been observed. See for example, Tuzi et al. (1994) Br J Cancer 69:417; Henkemeyer et al. (1994) Oncogene 9:1001; and Pandey et al. (1995) Curr Biol 5:986. These studies provide appropriate guidance for one of ordinary skill in the art to recognize that the binding activity, for example, resides in the extracellular domains of each of the receptor and ligand.

The art is replete with examples of combinatorial techniques for identifying fragments of a proteins, such as Ephs and Ephrins, which retain a particular biological activity of the full length protein, such association in protein complexes. At the time of the instant invention, combinatorial techniques for generating and processing libraries of variants of a protein were routine in the art,

even for libraries exceeding a billion different variants. Exemplary mutagenic techniques include alanine scanning mutagenesis and the like (Lowman et al. (1991) Biochemistry 30:10832-10838; and Cunningham et al. (1989) Science 244:1081-1085), by linker scanning mutagenesis (Brown et al. (1992) Mol. Cell Biol. 12:2644-2652; McKnight et al. (1982) Science 232:316); by saturation mutagenesis (Meyers et al. (1986) Science 232:613); by PCR mutagenesis (Leung et al. (1989) Method Cell Mol Biol 1:11-19); or by random mutagenesis (Miller et al. (1992) A Short Course in Bacterial Genetics, CSHL Press, Cold Spring Harbor, NY) in order to create libraries of variants which can be screened for a given biological activity. In addition, the Ladner et al. PCT publication WO90/02809, the Goeddel et al. U.S. Patent 5,223,408, and the Markland et al. PCT publication WO92/15679 illustrate specific techniques which one skilled in the art could utilize to generate libraries of Eph or Ephrin variants which can be rapidly screened to identify fragments which retained a particular activity such as protein binding. These techniques are exemplary of the art and demonstrate that large libraries of related truncants can be generated and assayed to isolate particular variants without undue experimentation.

Such techniques have been applied to other members of the Eph/Ephrin families. Labrador et al. (1997) EMBO J 16:3889, for example, determined the domains of several Eph receptors responsible for ligand binding by constructing a series of Eph receptor deletion, including soluble deletion mutants, and domain swapping mutants, which were then analyzed for ligand binding and subsequent receptor signaling. They concluded that "the same domain is used by all Eph receptors to interact with their respective ligand sublasses". Labrador et al., at page 3890.

Indeed, the working examples of the present application include the use of a soluble EphB2 Fc fusion protein. See, for example, Example 13 of the instant application.

It is plain from the combinatorial mutagenesis art that it was in fact routine for those skilled in the art to engage in large scale truncation of proteins, without any preconceived ideas of which residues were critical to the biological function, and generate wide arrays of variants having equivalent biological activity. Indeed, it is the ability of combinatorial techniques to screen billions of different variants by high throughout analysis that removes any requirement of *a priori* understanding or knowledge of critical residues.

The only inventive step(s) required to generate the assays using portions of Eph and Ephrin proteins useful in the instant claims have already been carried out by the Applicants. Routine screening techniques taught in the specification and available in the art at the time the present invention was made provide sufficient guidance for identifying other fragments for use in the subject invention. Accordingly, Applicant asserts that the specification, in light of the art at the time the present invention was made, is enabling for a sufficient number of permutations of the invention to entitle Applicant to the invention as presently claimed.

Finally, the Examiner has rejected claims 48-50 and 114-150 as not being enabled for embodiments of the assay which identify agents which enhance the interaction between Eph and Ephrin proteins. The Examiner argues that "while blocking the interaction between two molecules...is art standard, enhancement of an interaction is less predictable". The basis for this argument is not understood by the Applicants. For the sake of argument, assuming that finding potentiators of an interaction is more unlikely, as the Examiner avers, the fact is that the subject application describes an assay in which the read-out can distinguish between agents which have no effect, agents which inhibit and agents which increase the binding.

The Federal Circuit has recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact findings and its ultimate action. Dickinson v. Zurko, 119 S. Ct. 1816 (1999). In light of the Applicants arguments of record, and the presumption in favor of the Applicants, it is respectfully asserted that the Examiner's maintenance of the present rejection is not supported by substantial evidence, and as such, does not meet the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact finding results which rebut the presumption in favor of the Applicants.

Rreconsideration and withdrawal of the rejection of the pending claims 35 USC § 112, first paragraph, is respectfully requested. In the absence of withdrawl, Applicants respectfully request that the Examiner provided the factual basis, including reference to the art or personal knowledge which is being relied upon to maintain the rejection.

III. THE PENDING CLAIMS COMPLY WITH 35 USC §112, 2ND PARAGRAPH

In view of the above amendments of the claims, which define "portions" of Eph and Ephrin proteins in terms of functional requirements, the rejection of the claims under 35 USC §112, 2nd paragraph is believed to be obviated.

IV. CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants hereby request that any fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: December 4, 2002

Customer No: 28120
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050

Matthew P. Vincent
Reg. No. 36,709

VERSION WITH MARKINGS TO SHOW CHANGES MADE

46. (**Twice Amended**) A method for assessing the ability of ~~identifying~~ an agent to interfere with blood vessel formation ~~that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is an Ephrin family ligand the venous cell-specific surface molecule is an Eph family receptor or a portion thereof~~, comprising:

(a) combining:

(1) a first polypeptide including at least a portion of an ~~the~~ Ephrin ~~family~~ ligand that interacts with an Eph receptor, ~~or a portion thereof;~~

(2) a second polypeptide including at least a portion of the Eph ~~family~~ receptor that interacts with said Ephrin ligand, said Ephrin ligand and/or Eph receptor being selected on the basis of being selectively expressed on one of either venous or arterial cells, ~~or a portion thereof~~; and

(3) an ~~the~~ agent ~~to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2)~~,

under conditions wherein said Eph receptor and Ephrin ligand portions of interact in the absence of said agent ~~appropriate for interaction between the molecule of (1) and the molecule of (2)~~;

(b) determining if said agent interferes with said interaction ~~the extent to which the molecule of (1) and the molecule of (2) interact~~; and

(c) for an agent that interferes with said interaction, further assessing the ability of said agent to interfere with blood vessel formation. ~~comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);~~

~~wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).~~

47. (**Twice Amended**) A method for identifying an agent that inhibits interaction of ~~an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is~~ EphrinB2 ~~or a portion thereof~~ and ~~the venous cell-specific molecule is~~ EphB4 ~~or a portion thereof~~, comprising:

(a) combining:

(1) an EphrinB2 protein or at least a portion thereof sufficient to interact with an EphB4 protein,~~;~~

(2) the EphB4 protein or at least a portion thereof sufficient to interact with said EphrinB2 protein,~~;~~ and

(3) an ~~the~~ agent ~~to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2)~~,

under conditions appropriate for interaction between said EphrinB2 and EphB4 proteins in the absence of said agent ~~the molecule of (1) and the molecule of (2)~~;

(b) determining the extent to which said EphrinB2 and EphB4 proteins~~the molecule of (1) and the molecule of (2)~~ interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ occurs in the absence of the agent ~~to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2)~~;

wherein if the extent to which interaction of said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of EphrinB2 and EphB4~~the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2)~~.

49. (**Twice Amended**) A method for identifying an agent that enhances interaction of ~~an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is~~ an Ephrin ~~family~~ ligand ~~or a portion thereof~~ and ~~the venous cell-specific surface molecule is~~ an Eph ~~family~~ receptor ~~or a portion thereof~~, comprising:

(a) combining:

(1) a first polypeptide including at least a portion of an ~~the~~ Ephrin ~~family~~ ligand that interacts with an Eph receptor, ~~or a portion thereof;~~

(2) a second polypeptide including at least a portion of the Eph ~~family~~ receptor that interacts with said Ephrin ligand, said Ephrin ligand and/or Eph receptor being selected on the basis of being selectively expressed on one of either venous or arterial cells ,~~or a portion thereof;~~ and

(3) an ~~the~~ agent ~~to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2)~~,

under conditions ~~appropriate for interaction between the molecule of (1) and the molecule of (2)~~ wherein said Eph receptor and Ephrin ligand portions of interact in the absence of said agent;

(b) determining the extent to which said first and second polypeptides ~~the molecule of (1) and the molecule of (2)~~ interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of said first and second polypeptides ~~the molecule of (1) and the molecule of (2)~~ occurs in the absence of the agent ~~to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2)~~;

wherein if the extent to which interaction of said first and second polypeptides ~~the molecule of (1) and the molecule of (2)~~ is greater in the presence of the agent than in the absence of the agent, the agent is one which enhances interaction of an Ephrin ligand and Eph receptor ~~the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2)~~.

50. (**Twice Amended**) A method for identifying an agent that enhances interaction of ~~an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the Ephrin family ligand is~~ EphrinB2 ~~or a portion thereof~~ and ~~the Eph family receptor is~~ EphB4 ~~or a portion thereof~~, comprising:

(a) combining:

(1) an EphrinB2 protein or at least a portion thereof sufficient to interact with an EphB4 protein,~~;~~

(2) the EphB4 or at least a portion thereof sufficient to interact with said EphrinB2 protein,~~;~~ and

(3) an ~~the~~ agent, ~~to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2),~~

under conditions appropriate for interaction between said EphrinB2 and EphB4 proteins in the presence of said agent ~~the molecule of (1) and the molecule of (2)~~;

(b) determining the extent to which said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ occurs in the absence of the agent ~~to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2)~~;

wherein if the extent to which interaction of said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ is greater in the presence of the agent than in the absence of the agent, the agent is one which enhances interaction of EphrinB2 and EphB4 ~~the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2)~~.

77. (**Amended**) The method of Claim ~~45~~ 46 or 49, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is selected from the group consisting of ~~a protein,~~ a soluble extracellular portion of said Ephrin ligand ~~a protein~~ and a fusion protein including an extracellular portion of said Ephrin ligand; and/or

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is selected from the group consisting of ~~a protein,~~ a soluble extracellular portion said Eph receptor ~~of a~~

~~protein~~ and a fusion protein including an extracellular portion of said Eph receptor.; ~~or~~

~~(c) both (a) and (b).~~

78. (**Amended**) The method of Claim ~~45~~ 46 or 49, wherein

~~(a)~~ the interaction of said first and second polypeptides ~~between the arterial cell-specific molecule and the venous cell-specific molecule~~ is determined by detecting binding of the first and second polypeptides ~~arterial cell-specific molecule~~, wherein at least one of the first and second polypeptides includes ~~the arterial cell-specific molecule comprises~~ a detectable label~~; or~~

~~(b) the interaction between the arterial cell-specific molecule and the venous cell-specific molecule is determined by detecting binding of the venous cell-specific molecule, wherein the venous cell-specific molecule comprises a label~~.

79. (**Amended**) The method of Claim 78 wherein the label ~~in (a) or the label in (b)~~ is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

80. (**Amended**) The method of any of Claims ~~45~~ 46, 47, 49, 50 and 151, wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

81. (**Amended**) The method of any of Claims ~~45~~ 46, 47, 49, 50 and 151, wherein the agent is an organic compound.

82. (**Amended**) The method of Claim ~~45~~ 46 or 49, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is expressed on a cell; and/or

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is expressed on a cell~~; or~~

~~(c) both (a) and (b)~~.

83. (**Amended**) The method of Claim ~~45~~ 82, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is expressed on an isolated arterial endothelial cell; and/or

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is expressed on an isolated venous endothelial cell. ~~; or~~

~~(c) both (a) and (b).~~

84. (**Amended**) The method of Claim ~~45~~ 46 or 49, wherein

(a) the Ephrin ligand ~~arterial cell-specific surface molecule~~ is selected on the basis of being selectively expressed on ~~a cell derived from an isolated~~ arterial endothelial cells; and/or

(b) the Eph receptor ~~venous cell-specific surface molecule~~ is selected on the basis of being selectively expressed on ~~a cell derived from an isolated~~ venous endothelial cells. ~~; or~~

~~(c) both (a) and (b).~~

85. (**Amended**) The method of Claim ~~45~~ 82, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is expressed on a cell which has been genetically modified to recombinantly express the first polypeptide ~~arterial cell-specific surface molecule~~; and/or

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is expressed on a cell which has been genetically modified to recombinantly express the second polypeptide. ~~venous cell-specific surface molecule; or~~

~~(c) both (a) and (b).~~

86. (**Amended**) The method of Claim ~~45~~ 46 or 49, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is conjugated to a solid support and the second polypeptide ~~venous cell-specific surface molecule~~ is diffusible; or

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is conjugated to a solid support and the first polypeptide ~~arterial cell-specific surface molecule~~ is diffusible.

87. (**Reiterated**) The method of Claim 86 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

88. (**Amended**) The method of Claim ~~46~~ 47, 50 or 151, wherein

~~(a)~~ the interaction between said EphrinB2 and EphB4 proteins ~~the molecule of (1) and the molecule of (2)~~ is determined by detecting binding of the EphrinB2 and EphB4 proteins ~~molecule of (1)~~, wherein at least one of said EphrinB2 and EphB4 proteins includes ~~the molecule of (1) comprises~~ a detectable label. ~~; or~~

~~(b) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (2), wherein the molecule of (2) comprises a label.~~

89. (**Amended**) The method of Claim 88 wherein the label ~~in (a) or the label in (b)~~ is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

92. (**Amended**) The method of Claim ~~46~~ 47, 50 or 151, wherein

(a) the EphrinB2 protein ~~family ligand or portion thereof~~ is expressed on a cell; and/or

(b) the EphB4 protein ~~family receptor or portion thereof~~ is expressed on a cell. ~~; or~~

~~(c) both (a) and (b)~~

93. (**Amended**) The method of Claim ~~46~~ 92, wherein

(a) the EphrinB2 protein ~~family ligand or portion thereof~~ is expressed on an isolated arterial endothelial cell; and/or

(b) the EphB4 protein ~~family receptor or portion thereof~~ is expressed on an isolated venous endothelial cell. ~~; or~~

~~(c) both (a) and (b).~~

95. (**Amended**) The method of Claim ~~46~~ 92, wherein

(a) the EphrinB2 protein ~~family ligand or portion thereof~~ is expressed on a cell which has been genetically modified to recombinantly express the EphrinB2 protein ~~family ligand or portion thereof~~,

(b) the EphB4 protein ~~family receptor or portion thereof~~ is expressed on a cell which has been genetically modified to recombinantly express the EphB4 protein ~~family receptor or portion thereof~~; or

(c) both (a) and (b).

96. (**Amended**) The method of Claim ~~46~~ 47, 50 or 151, wherein

(a) the EphrinB2 protein ~~family ligand or portion thereof~~ is conjugated to a solid support and the EphB4 protein ~~family receptor or portion thereof~~ is diffusible; or

(b) the EphB4 protein ~~family receptor or portion thereof~~ is conjugated to a solid support and the EphrinB2 protein ~~family ligand or portion thereof~~ is diffusible.

97. (**Reiterated**) The method of Claim 96 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

98. (**Amended**) The method of Claim ~~46~~ 47, 50 or 151, wherein ~~wherein (a) the~~ at least one of said EphrinB2 protein and ~~family ligand or portion thereof is a fusion protein; (b) the~~ EphB4 protein ~~family receptor or portion thereof~~ is a fusion protein. ~~; or~~

~~(c) both (a) and (b).~~

99. (**Amended**) The method of Claim 98 wherein ~~(1)~~ the fusion protein includes ~~in (a) comprises~~ an Fc domain. ;

~~(2) the fusion protein in (b) comprises an Fc domain; or~~

~~(3) both (1) and (2).~~

100. (**Amended**) The method of Claim 98 wherein the fusion protein is soluble.

~~(1) the fusion protein in (a) comprises an Fc domain of an IgG molecule;~~

~~(2) the fusion protein in (b) comprises an Fc domain of an IgG molecule; or~~

~~(3) the fusion protein in (a) and (b) comprises an Fc domain of an IgG molecule.~~

107. (**Amended**) The method of Claim 47, 50 or 151, wherein

(a) the EphrinB2 protein ~~or a portion thereof~~ is expressed on a cell ~~derived from an isolated arterial endothelial cell~~; and

(b) the EphB4 protein ~~or a portion thereof~~ is a soluble protein including an extracellular fragment of EphB4 which binds to the EphrinB2 protein. ~~expressed on a cell derived from an isolated venous endothelial cell; or~~

~~(c) both (a) and (b).~~

108. (**Amended**) The method of Claim 47, 50 or 151, wherein

(a) the EphrinB2 protein ~~or a portion thereof~~ is a soluble protein including an extracellular fragment of EphrinB2 which binds to the EphB4 protein ~~expressed on a cell which has been genetically modified to express EphrinB2 or a portion thereof~~; and

(b) the EphB4 protein ~~or a portion thereof~~ is expressed on a cell which is contacted with said EphrinB2 protein and agent. ~~has been genetically modified to express EphB4 or a portion thereof; or~~

~~(c) both (a) and (b).~~

114. (**Amended**) The method of Claim ~~48~~ 46 or 49, wherein

(a) the first polypeptide ~~arterial cell specific surface molecule~~ is a soluble protein including an extracellular fragment of the Ephrin ligand which binds to the Eph receptor ~~selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein~~;

(b) the second polypeptide ~~venous cell specific surface molecule~~ is expressed on a cell which is contacted with said first polypeptide and agent. ~~selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein;~~

120. (**Amended**) The method of Claim ~~48~~ 46 or 49, wherein

(a) the first polypeptide ~~arterial cell-specific surface molecule~~ is expressed on a ~~an isolated arterial endothelial~~ cell;

(b) the second polypeptide ~~venous cell-specific surface molecule~~ is a soluble protein including an extracellular fragment of the Eph receptor which binds to the Ephrin ligand. ~~expressed on an isolated venous endothelial cell; or~~

~~(c) both (a) and (b).~~

151. (**New**) A method for identify an agent having an anti-angiogenic activity

(a) combining

an EphrinB2 protein, or a portion thereof that interacts with EphB4, and

an EphB4 protein, or a portion thereof that interacts with EphrinB2,

wherein said EphrinB2 and EphB4 proteins interact to form a ligand-receptor complex;

(b) determining if a test agent can interfere with a function of said ligand-receptor complex; and

(c) for said test agent that interferes with said ligand-receptor complex, administering said agent to a nonhuman animal and measuring the antiangiogenic activity, if any, of said agent.

152. (**New**) The method of Claim 47, 50 or 151, wherein at least one of the EphrinB2 protein and EphB4 protein are expressed on cultured cells, and the agent is added to culture medium in which the cells are placed.

153. (**New**) The method of Claim 46 or 49, wherein at least one of the first and second polypeptides are expressed on cultured cells, and the agent is added to culture medium in which the cells are placed.

154. (**New**) The method of Claim 46, wherein the step of further assessing the ability of said agent to interfere with blood vessel formation includes administering said agent to a nonhuman animal and determining if the agent affects arterial or venous structures.

155. (**New**) The method of Claim 46, wherein the step of further assessing the ability of said agent to interfere with blood vessel formation includes adding said agent to a cell culture containing arterial endothelial cells and venous endothelial cells and determining if the agent affects growth or differentiation of said cells.